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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/376,317	08/18/1999	KENNETH B. STOKES	P-3569CON	6342

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EXAMINER
BECKERLEG, ANNE M

ART UNIT	PAPER NUMBER
1632	

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19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/376,317	Applicant(s) STOKES ET AL.	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-14,20-25,39-42 and 48-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-14,20-25,39-42 and 48-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/29/02 has been entered. The applicant requests the cancellation of claims 15-19, 43-47, and 51-61. Please note that claims 15-19, 43-47, and 51-54, and 61 were canceled at the request of the applicant in applicant's previous response received on 9/4/01. Further, claims 55-60 were canceled at the request of the applicant in applicant's response received on 11/6/00. Claims 1, 4-14, 20-25, 39-42, and 48-50 are pending and active in the instant application. An action on the merits follows.

The text of those sections of Title 35 , US code, not included in this office action may be found in previous office actions.

The applicant's arguments submitted in conjunction with the RCE on 4/19/02 are a copy of those previously submitted on 9/4/01, paper no. 10. These claim amendments and arguments were addressed in detail in the final office action mailed on 12/19/01, paper no. 11. Applicant's

have not submitted any new claim amendments or arguments. The rejections and arguments presented by the examiner in paper no. 11 are reiterated below.

Claim Rejections - 35 USC § 112

The rejection of claims 1, 4-14, 20-25, 39-42, and 48-50 under 35 U.S.C. 112, first paragraph, for lack of written description has been withdrawn in view of applicant's amendments to the claims limiting the conduction protein to Cx40, Cx43, and Cx45.

The rejection of claims 1, 4-14, 20-25, 39-42, and 48-50 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant argues that since the claims have been further rejected under 35 U.S.C. 103 as being obvious, it is difficult to reconcile the office's position that the invention is non-enabled. The rejection of the claims under 35 U.S.C. 112, first paragraph, for lack of enablement is not in conflict with the rejection of the claims under 35 U.S.C. 103(a) for non-obviousness. The specification on page 5 clearly discloses that the intended use for the claimed delivery methods is for the treatment and/or correction of disturbances in the cardiac conduction pathway. It is also noted that claims 10-11 and 20-23 recite that a "therapeutically" effective amount of protein is

delivered to the cardiac tissues. The specification does not provide an enabling disclosure for the delivery of therapeutically effective amounts of any conduction protein to cardiac tissues using any genetic material including nucleic acid vectors such that any effect on cardiac conduction is observed. Thus, the rejection under 112 is based on "how to use" the invention as disclosed in the instant specification. 35 U.S.C. 112, first paragraph. Case law states that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991), emphasis added.

In regards to the rejection of the 1, 4-9, 12-14, 24-25, 39-42 under 35 U.S.C. 103, please note that the previous office action, paper no. 7, did not maintain this rejection over claims 10-11 and 20-23 which recite that the delivery method delivers "therapeutically effective" amounts of the recombinant nucleic acid vectors. The applicant's delivery system as claimed in claims 1, 4-9, 12-14, 24-25, 39-42 does not recite the limitation that the delivered genetic material has any effect on the cardiac tissue. The claims simply recite the delivery of genetic material to cardiac tissue. The intended use of the delivery method disclosed in the specification as the treatment of conduction disturbances does not have patentable weight for the purposes of prior art. Further, the office has not indicated that the prior art cited in the 103 rejection is enabling for the treatment of cardiac disease. Therefore, there is no conflict between the instant enablement rejection of the claims for "how to use" the invention as disclosed in the specification for treating conduction

disturbances and the rejection of the claims under 103 based on the recited method steps which do not include a recitation of therapeutically effective delivery.

The previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). The applicant has not provided any arguments concerning the specific grounds of rejection discussed in the previous office action. The instant grounds of rejection have been reiterated below for applicant's convenience.

The specification does not provide sufficient guidance for genetic material encoding any conduction protein that can have any therapeutic effect on cardiac conduction when delivered using the instant methods. The specification provides prophetic exemplifications for the isolation and purification of nucleic acid molecules encoding the connexin proteins and insertion of connexin cDNA into plasmid and adenoviral vectors. The specification also provides general

guidelines on recombinant DNA production including lists of potential promoters and polyadenylation signals, and incorporates by reference the coding sequences for the connexins Cx40, Cx43, and Cx45. The specification fails to provide any guidance as to the identity, sequence, or biological properties of any conduction proteins other than the connexin family members listed above. Further, the specification fails to provide any guidance as to characteristics of genetic material encoding any conduction protein for use in the instant delivery system other than nucleic acid vectors. In regards to the use of vectors such as viral or adenoviral vectors disclosed by the specification, the specification fails to provide essential teachings on the method of delivery genetic material from said catheter delivery device such that any electrical energy generated by the device would not adversely impact the ability of the vectors to transduce cells in the cardiac tissue or damage the vector's stability and ability to express the encoded transgene. The specification does not disclose to what extent the administration of an electric field from the applicant's device will effect the quantity, structural integrity, and biological properties of DNA or RNA delivered into the cells as a result of any increase in the permeation of the cell membrane. It is well known in the art that the administration of an electric field, such as in the use of electroporation, can result in a significant level (e.g. 40-80%) of cell lysis (e.g. See Weaver et al., US Patent 5,019,034, column 3, lines 44-64). The specification also fails to disclose the manner and ability of any genetic material to transduce cardiac tissue cells which have been damaged due to the use of a helical electrode which is screwed into the myocardium.

In addition to the lack of guidance concerning the identity of conduction proteins for use in the instant invention other than connexins, the identity of genetic material other than nucleic acid vectors, the effects of the claimed catheter delivery device on the ability of the cardiac tissue to take up foreign genetic material and the effects of the device on the ability of the genetic material to express any encoded protein as noted above, the specification fails to provide guidance as to the level of cardiac cell transformation, the types of cardiac cells transformed, and the level of expression of any conduction protein from any delivered genetic material that correlates with any effect on conduction in cardiac tissue in vitro or in vivo. The specification's sole disclosure of conduction proteins are members of the connexin family. At the time of filing, Kanter et al. discloses that the three members of the connexin gap junction family, Cx40, Cx43, and Cx45, have different biophysical properties, and that in combination they are believed to be important in the regulation of cellular coupling . Further, these proteins have regional differences in expression with the various cardiac tissues, such as the Purkinje fibers and ventricular myocytes, and they are not expressed in one-to-one-to-one ratios with any cardiac tissue (Kanter et la., page 861, columns 1-2, and page 866). The specification does not provide sufficient guidance that the expression of any level of any one connexin family member in any type of cardiac cell would have any effect on cardiac conductance. In view of the different biological properties of the connexin family members, the complex interactions between the family members that results in gap formation and cellular coupling, and the differential cellular distribution of the connexin family

members, the skilled artisan would not have been able to predict whether the introduction of any connexin family member into any cardiac cell would result in any effect on cardiac conduction.

Furthermore, at the time of filing, the art did not consider the delivery and expression of therapeutic genes using nucleic acid expressions systems including viral vectors to be predictable. Verma et al. teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2).Verma points out that, " [t]here are considerable immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression", that, " [a] critical limitation of retroviral vectors is their inability to infect non-dividing cells, such as those that make up muscle, brain, lung, and liver tissue " (Verma et al. (1997) Nature, Vol. 389, page 240, column 1, paragraph 3, and page 241, column 2, paragraph 2). Verma also teaches that the choice of an appropriate enhancer-promoter combination is critical to the level and consistency of gene expression from a particular vector and that , " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1). Marshall et al. concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall et al. (1995) Science, Vol. 269, page 1054, column 3, paragraph

2, and page 1055, column 1). Orkin et al. further states, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4, and page 8, paragraph 2,). Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression using nucleic acid vectors, the breadth of the claims, and the lack of guidance provided by the specification for the parameters affecting gene delivery and expression using the instant catheter delivery device, it would have required undue experimentation to practice the invention as claimed and the skilled artisan would not have predicted success in treating cardiac conduction disturbances by administering any genetic material encoding any conduction protein to cardiac tissue using the instant delivery methodology.

The rejection of claim 25 under 35 U.S.C. 112, second paragraph, for indefiniteness has been withdrawn in view of applicant's amendment to the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 4-9, 12-14, 24-25, 39-42 under 35 U.S.C. 103(a) over Mulier et al. in view of Leiden et al. and Kanter et al. is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that since the catheter disclosed by Mulier et al. is an ablation catheter, Mulier et al. teaches away from using the catheter to deliver genetic materials for the purpose of providing new conductive proteins to establish new cellular tissue. This argument was presented by the applicants in the previous response, paper no. 6, and was addressed in detail in the previous office action, paper no. 7. In short, the applicant's delivery system as claimed does not recite the limitation that the delivered genetic material has any effect on the cardiac tissue. The claims simply recite the delivery of genetic material to cardiac tissue. The intended use of the delivery method disclosed in the specification as the treatment of conduction disturbances does not have patentable weight for the purposes of prior art. As discussed in detail in the previous office actions, the combination of references cited provides motivation for using the catheter system taught by Mulier to deliver genetic material to cardiac tissue as taught by Leiden. Further, the skilled artisan would not consider the presence of tissue damage near the site of administration of genetic material as an obstacle to the transfection of nearby living cells. Therefore, as the limitation that the delivered genetic material must have a therapeutic effect on cardiac conduction

is not recited by the instant claims, the applicant's arguments are not found persuasive and the rejection is therefore maintained.

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé